# Duloxetine-Related Acute Dysphoria

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## ABSTRACT

Duloxetine is the newest addition to the US antidepressant market. In this case series, we describe what appears to be an unusual adverse reaction to duloxetine: an acute dysphoric response. This response occurred in five patients (four women and one man, all outpatients, ages 37–73 years) and manifested with either the initiation of the medication or during a dosage increase (all doses were 60mg per day or less). Among all patients, this unexpected response promptly subsided with either a dosage reduction or discontinuation of the medication. These observations suggest that a small minority of patients taking duloxetine may develop acute and dysphoric responses to the medication, which may be addressed with either a dosage reduction or discontinuation of duloxetine.

## INTRODUCTION

Duloxetine (Cymbalta™) is a relatively new antidepressant that exerts a potent and balanced (i.e., dual) inhibition of both serotonin and norepinephrine reuptake. The drug is well absorbed after oral administration, has a half-life of

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approximately 12 hours, and is extensively metabolized by the liver. Duloxetine is the only antidepressant that is approved by the US Food and Drug Administration (FDA) for the treatment of major depression as well as pain—specifically, diabetic peripheral neuropathy.

In our clinical experience, we have encountered a small number of patients who have reported acute, intense, and dysphoric reactions while taking duloxetine, particularly with dosage increases. While the *Clinical Psychopharmacology* database[1] describes agitation and irritability as possible side effects of duloxetine, the adverse responses that we report are, in our opinion, more dramatic and severe.

## CASE REPORTS

For all of the cases in this series, the first author initiated the prescription for duloxetine. Duloxetine was prescribed for depressive symptoms, either major depression, dysthymia, or both, although some patients may have had additional psychiatric comorbidity (e.g., anxiety) that might have been effectively treated with antidepressant medications. Because all of these patients underwent an evaluation for depression, each was screened for bipolar disorder and none reported any past hypomanic or manic episodes.

**Case 1.** Ms. L was a 44-year-old Caucasian woman who suffered for years from both anxiety and depressive symptoms. Her anxiety symptoms, which pre-dated the depressive symptoms, began when the patient was in her early 30s. The family history included two other relatives with anxiety syndromes. Ms. L began antidepressant therapy at age 39 and had previously been prescribed citalopram, escitalopram, venlafaxine extended release, fluoxetine, sertraline, and bupropion—all with partial symptom resolution. She reported no pain syndrome, but suffered from gastroesophageal reflux and was prescribed pantoprazole. At the time of psychiatric evaluation in 2003, following the ending of an intimate relationship, she was diagnosed with major depression (single episode), late-onset dysthymic disorder, generalized anxiety disorder, and panic disorder with agoraphobia using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). She began treatment with venlafaxine extended release and sustained a very good response for nearly three years. Because of a moderate loss of efficacy over time with venlafaxine extended release, Ms. L decided to discontinue the medication and was successfully weaned of the drug over several weeks. After a two-day medication-free period, in January of 2006, Ms. L was started on 20mg of duloxetine per day, which was increased to 40mg per day after one week. At the end of two weeks of duloxetine exposure, the patient emphatically acknowledged acute and intense dysphoria with irritability. She promptly stopped the medication and symptoms resolved within 48 hours. Subsequently, the patient requested re-treatment with venlafaxine extended release in combination with buspirone augmentation.

**Case 2.** Mrs. M, a 73-year-old Caucasian woman, unexpectedly lost her husband following an acute myocardial infarction, which occurred during a vacation in Arizona. Afterwards, she was evaluated for depression by her family physician and referred for psychiatric consultation without psychotropic medication treatment. The history indicated that within the extended family, there were no members with histories of psychiatric treatment, exposure to psychotropic medications, suicide attempts/completions, or alcohol/substance abuse. Mrs. M was diagnosed with DSM-IV major depression (single episode) as well as chronic knee pain. She underwent a course of antidepressant treatment with escitalopram at 20mg per day with a modest response. She was eventually switched to venlafaxine extended release but promptly experienced an unacceptable increase in blood pressure. The venlafaxine extended release was discontinued after three weeks. In June of 2006, Mrs. M began treatment with duloxetine at 20mg per day. In July of 2006, after several days on an increased dosage of 40mg per day, Mrs. L described an acute and intense dysphoric response to the medication. She stated, "I have never felt this depressed in all my life." The duloxetine was promptly discontinued and her dysphoric state resolved within 48 hours. Afterwards, she requested a return to treatment with escitalopram, which again offered modest benefit.

**Case 3.** In September of 2006, Mrs. O, a 51-year-old Caucasian woman, was referred by her family physician for the treatment of depressive symptoms. Mrs. O reported a longstanding history of smoldering depression that was punctuated by acute depressive episodes. The family history included multiple members with alcohol and substance abuse as well as bipolar disorder and a completed suicide. Mrs. O had previously been treated with fluoxetine, bupropion extended release, sertraline, citalopram, and escitalopram. She had seen a psychiatrist on only one occasion; the bulk of her psychotropic medications had been prescribed by her family physician. The psychiatric consultation was precipitated by acute inflammatory neurological damage, which Mrs. O sustained to her right upper extremity, particularly her thumb. She was diagnosed with Parsonage Turner Syndrome (brachial neuritis) and wore a thumb splint. Her reduced thumb mobility greatly affected her ability to work on a computer, which was essential for Mrs. O's job. At the time of psychiatric consultation, Mrs. O was diagnosed with DSM-IV recurrent major depression, late-onset dysthymic disorder, and Parsonage Turner Syndrome. She had already been taking duloxetine for several months and reported

modest benefit. At the time of consultation, her duloxetine dosage was increased from 40mg to 60mg per day. Within 48 hours, the patient reported feeling very irritable, acutely agitated, and, "depressed like I have never felt before." The patient resumed treatment with the 40mg dose of duloxetine without any further adverse reaction.

**Case 4.** Mr. K was a 37-year-old Caucasian man who presented for the evaluation of both depressive symptoms and obsessive preoccupation with rituals. He suffered from gastroesophageal reflux, sleep apnea, and year-round allergies. The family history included depression as well as alcohol abuse. Mr. K had never been seen by a psychiatrist or prescribed psychotropic medication. At evaluation in February of 2006, Mr. K was diagnosed with DSM-IV early-onset dysthymic disorder, obsessive-compulsive disorder, and obsessive-compulsive personality disorder. Following evaluation, he underwent separate treatment trials with low doses of sertraline, venlafaxine extended release, and citalopram. Unfortunately, Mr. K experienced unacceptable side effects, even at very low doses of psychotropic medication. For example, he reported extreme emotional apathy and indifference with both sertraline and citalopram, and impairing fatigue with venlafaxine extended release. Although he had no comorbid pain syndrome, he was prescribed duloxetine 20mg per day in April of 2007. He had been off all psychotropic medications for several weeks. Within two weeks, the patient began to acutely experience, "a heavy feeling, zoned out, it puts me in a negative spin." These adverse effects promptly dissipated within 48 hours of discontinuing duloxetine.

**Case 5.** Mrs. W was a 43-year-old Caucasian woman who was referred by her family physician because of chronic smoldering depression that was superimposed with episodes of acute and intense depression. The family history included depression, alcohol abuse, paranoid schizophrenia, and a completed suicide. At evaluation, Mrs. W was diagnosed with DSM-IV recurrent major depression and early-onset dysthymic disorder. Following evaluation, Mrs. W was prescribed sertraline with an initially good response. However, with time, her response waned and she was augmented with separate courses of buspirone, topiramate, and gabapentin. During her course of treatment, she acutely developed diffuse joint pain. She inquired about duloxetine, gradually weaned off sertraline, and after a five-day drug-free period, was started on a monotherapy trial with duloxetine 20mg per day in May of 2007. Eleven days later, the patient stated, "Not only do I not seem to be feeling any improvements, but I'm actually feeling worse. My joints aren't any better at all and…I can't even stand to be around myself! I am so grumpy, irritable and sad and it seems to be worsening each day. This is probably the worst I've felt since the first time I 'bottomed out' with my depression." Within 48 hours of duloxetine discontinuation, the patient's acute dysphoria dissipated. She elected to return to treatment with sertraline and her psychiatric symptoms significantly improved.

## DISCUSSION

Duloxetine is a relatively new product to the antidepressant market. To date, we are not aware of any case reports that describe acute and intense dysphoric reactions to the drug. In our small case series, two patients experienced these reactions with drug initiation and three with dosage increases. These observations suggest that an acute dysphoric response to duloxetine may occur at any dose or time, not just with the initiation of treatment.

The explanation for these unexpected responses to duloxetine remains unknown. Importantly, none of the preceding patients were on doses above 60mg per day. In healthy volunteers, at doses of 60mg per day, duloxetine functioned as a serotonin reuptake inhibitor, with no evident effect on norepinephrine reuptake,[2] which is in contrast to the notion of a balanced inhibition effect. Studies support the presence of a dual neurotransmitter effect at higher doses,[3] an effect that appears to be more potent than those exerted by venlafaxine on serotonin and norepinephrine transporters.[4] The dosage range in this case series suggests that the dysphoric effect may relate to serotonergic mechanisms, but this is purely speculative at this juncture.

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One patient in our case series developed brief suicidal ideation. As for all antidepressants, the FDA requires a black box warning for duloxetine that details an increased risk of suicidality in children and adolescents. However, Acharya and colleagues[5] found that there were no significant differences in the incidence of suicide-related events between duloxetine and placebo.

While we encountered no cases in the PubMed or PsycINFO databases describing acute dysphoric responses

to duloxetine, there are two case reports[6,7] of patients with post-traumatic stress disorder whose symptoms worsened with duloxetine treatment. Whether trauma histories are or will be predictive of unusual adverse responses to duloxetine is unknown.

## CONCLUSION

To conclude, one possible adverse event associated with duloxetine treatment appears to be acute and intense dysphoric reactions. These reactions appear to exceed the irritability and agitation that are presently listed as possible side effects of duloxetine. They appear to promptly resolve with duloxetine reduction or discontinuation.

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